PCT/IB2003/003475

Translation

PATENT COOPERATION TREATY

PCT

525324

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1503	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/IB2003/003475	International filing date (*day/month/year*) 22 August 2003 (22.08.2003)	Priority date (*day/month/year*) 22 August 2002 (22.08.2002)
International Patent Classification (IPC) or national classification and IPC A61K 45/00, 31/519, 31/55, 31/7088, 39/395, 48/00, A61P 17/04, 43/00, C07D 401/14, 403/06, 417/14, 471/14, 519/00		
Applicant KYOWA HAKKO KOGYO CO., LTD.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☒ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) 1 DISKETTE, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19 March 2004 (19.03.2004)	11 August 2004 (11.08.2004)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

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International application No.
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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is language of a translation furnished for the purpose of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ The international application as originally filed/furnished

☐ the description:

pages _____, as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

pages _____, as originally filed/furnished

pages* _____, as amended (together with any statement) under Article 19

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the drawings:

pages _____, as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. 1, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis that of:

   a. type of material

   ☐ a sequence listing

   ☒ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purpose of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

** If item 4 in Box No. I applies, the listing and /or table(s) related thereto, which form part of the basis of the report, may be marked "superseded".*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 13, 17-19

because:

☒ the said international application, or the said claims Nos. 13, 17-19 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See supplemental sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 13, 17-19 .

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ see Supplemental Box for further details.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of III. 1.

The inventions set forth in claims 13 and 17-19 pertain to methods for treatment of the human body by therapy. (PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv))

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   See supplemental sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____ .

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

The technical feature shared by claims 1-3 and 12, claims 15 and 16 as they refer to claims 1-3, and claims 20-22, is prevention or treatment of itching which includes as an active ingredient a substance which suppresses signal transduction-related functions of a protein having the amino acid sequence presented in SEQ ID NO: 11. The technical feature shared by the inventions set forth in claims 4-11 and 14 and of claims 15 and 16 as they refer to claim 10, on the other hand, is compounds represented by formula (I) as such.

There is thus no technical feature shared by these two groups of inventions that can be regarded as a special technical feature, and the two groups are not so linked as to form a single general inventive concept.

It should be noted that no international search report has been prepared for the inventions set forth in claims 13 and 17-19, and for this reason they are not mentioned as inventions above.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-12, 14-16, 20-22	YES
	Claims		NO
Inventive step (IS)	Claims	4-11, 14	YES
	Claims	1-3, 12, 15, 16, 20-22	NO
Industrial applicability (IA)	Claims	1-12, 14-16, 20-22	YES
	Claims		NO

2. Citations and explanations

This opinion is presented with reference to documents 1 to 8 below, cited in the international search report, and documents 9 and 10, cited for the first time in this opinion.

Document 1: WO 02/24222 A2 (The Cleveland Clinic Foundation)

Document 2: M. H. Beers *et al.*, "The Merck manual of diagnosis and therapy", 17th edition, 1999, ISBN 0911910-10-7, ISSN 0076-6526, pp. 786-793

Document 3: WO 02/061087 A2 (Lifespan Biosciences, Inc.)

Document 4: M. Heiber *et al.*, DNA Cell Biol., 1995, 14 (1), pp. 25-35

Document 5: M. S. Mahadevan *et al.*, Genomics, 1995, 30, pp. 84-88

Document 6: EP 549352 A2 (Kyowa Hakko Kogyo Co., Ltd.)

Document 7: EP 325755 A1 (Kyowa Hakko Kogyo Co., Ltd.)

Document 8: JP 9-40662 A (Kyowa Hakko Kogyo Co., Ltd.)

Document 9: JP 2001-324495 A (Kobayashi Pharmaceutical Co., Ltd.)

Document 10: Michinori Kubo *et al.*, Yakugaku Zasshi, 1997, 117 (4), pp. 193-201

Claims 1-3, 12, 15, 16 and 20-22

It is known from Document 1 that administration of an efficacious quantity of a GPR4 antagonist is efficacious in the management of atopic dermatitis, and that SPC contributes to atopic dermatitis, causing exacerbation. Comparing the inventions set forth in claims 1-3, 12, 15, 16 and 20-22 with the disclosures in document 1 at this point, they differ in that the disease to which the former apply is itching whereas in the latter case it is atopic dermatitis, in that the former are restricted to specific agonists such as amino acid sequences which are recognized by an antibody whereas in the latter case there is no restriction, and in that the former claim the use of animals in a method for screening therapeutic agents whereas the latter discloses a system using cultured cells.

However, as document 2 also indicates, it is well known in the art that itching is a typical symptom of atopic dermatitis and, therefore, a person skilled in the art would not need special creative skill to use a GPR4 agonist, which is claimed to be efficacious against atopic dermatitis, in the management of itching.

Similarly, as regards the restriction to specific agonists, the entire amino acid sequence of GPR4 has been determined, and it is also known from documents 3 to 5 that antibodies and the like can be selected as antagonists thereof. Therefore, selection thereof is merely a suitable option available to a person skilled in the art.

Furthermore, a person skilled in the art would naturally recognize that SPC, which contributes to the worsening of atopic dermatitis, will also contribute to the worsening of itching; and as disclosed in documents 9 and 10, methods for screening constituents useful for the management of itching are known which include a step of

subcutaneous or intradermal administration into an animal of a substance which induces scratching behaviour, a step of subcutaneous or intradermal administration into the animal of the test compound, a step of measuring the number of occurrences of scratching behaviour, a step of comparing the number of occurrences of scratching behaviour with and without the test compound, and a step of selecting substances which decrease the number of occurrences of scratching behaviour. Given this, a person skilled in the art would not require special inventive skill to use SPC as the substance inducing scratching behaviour in a method disclosed in document 9 or 10, to give a specific method for screening agents for treating itching.

Therefore, the inventions set forth in claims 1-3, 12, 15, 16 and 20-22 do not involve an inventive step in the light of the disclosures in documents 1 to 5, 9 and 10.

Claims 4-11 and 14

Documents 6 to 8 disclose tricyclic compounds useful as medicaments.

However, these compounds all differ in chemical structure from the compounds described in these claims; moreover, they do not share a specific application, and they are not known to be especially associated with GPR4. Therefore, it cannot be said that a person skilled in the art could easily deduce the inventions set forth in these claims from the disclosures in these documents.

The inventions set forth in claims 4-11 and 14 thus involve an inventive step relative to documents 1 to 10.